Aberrant Antigen Expression in Patients with Acute Leukemias; Experience of King Hussein Medical Center in Jordan

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ABSTRACT

Objective: To assess the frequency of aberrant antigens expression in acute leukemias and their possible prognostic significance in a group of Jordanian patients.

Methods: A retrospective study of acute leukemia cases was conducted at King Hussein Medical Centre over 3 years (January 2012 to December 2014). A total of 368 cases of acute leukemia diagnosed by multi parameter flow cytometry performed on peripheral blood and/ or fresh bone marrow aspirates. The co-expression of myeloid markers on lymphoblasts and lymphoid markers on myeloblasts was analyzed. The findings were correlated with remission status.

Results: 368 cases of acute leukemias were retrieved; these were: 192 (52%) cases of acute myeloid leukemia (AML), 173 cases (47%) of acute lymphoblastic leukemia (ALL) and 3 cases (1%) with mixed phenotype acute leukemia. Aberrant immunophenotype expression was observed in 44 (23%) AML cases and in 50 (29%) of ALL cases. CD7 was the commonest aberrant lymphoid marker expressed in AML which was noted in 19/44 (43%). Of the aberrant B-ALL cases, CD33 were expressed in 18/38 (47%) and CD13 in 14/38 (37%). 212 out of 368 cases (58%) were followed up in our centre during treatment program and stratified into remission and non-remission groups based on morphologic assessment of peripheral blood and bone marrow aspirates. These tests were carried out at day 21 of induction therapy, completion of treatment and any clinical deterioration during the study period. 70% of non-remission ALL and 53% of non-remission AML had aberrant phenotypes. No significant differences were noted between classical and aberrant acute leukemias regarding age, sex and blasts count.

Conclusion: The incidence of aberrant antigen expression in acute leukemia was comparable with most published international data. Such aberrant antigen expression may represent a poor prognostic indicator among this group of Jordanian patients. These findings may help to recognize patients with high risk group and low remission rate. Further studies are needed to confirm the correlation between aberrant phenotypes with prognosis and therapeutic response of acute leukemia.

Key words: Aberrant phenotypes, Acute leukemia, Flow cytometry, Induction therapy

Introduction

Acute leukemia comprises a heterogenous group of malignancies with variable clinical, morphologic, and immunophenotypic

features.[1,2] Leukemias, both acute and chronic, account for 8% of all human cancers with a prevalence rate of approximately 4 million new cases diagnosed per year in developed countries.[3] National Cancer Institute, USA estimates the incidence of new leukemia cases was 13.3 per 100,000 people in United States.[4] Rapid and accurate diagnosis of acute leukemia is mandatory for appropriate treatment and predicting prognosis.[5]

In modern practice, immunophenotyping plays a crucial role in diagnosis and classification of acute leukemia, predicting response to different treatment modalities, monitoring minimal residual disease, prognostic evaluation and predicting patients survival.[3]

Acute leukemia is generally classified as acute lymphoid leukemia (ALL), acute myeloid leukemia (AML) and mixed phenotype acute leukemia (MPAL). In each type of acute leukemia, blast cells express characteristic patterns of markers known as cluster of differentiation antigens (CD), which can be detected by flow cytometry method.[6] Classification of acute leukemia depends on expression of lineage specific markers on blast cells. Recently, multi parameter flow cytometry has been developed to detect lineage characteristics of different subtypes of acute leukemia. [3] However, in several cases of acute leukemia, blasts of one lineage do not exhibit the markers of normal differentiation but expressed unusual markers in which myeloid associated antigens expressed in lymphoblasts and lymphoid associated antigen expressed in myeloblasts. This phenomenon is called aberrant phenotypes.[1,3,6]

The World Health Organization (WHO) 2008 Classification of Hematopoietic neoplasms relies on the morphologic, immunophenotypic, cytogenetic, and molecular features for the diagnosis and sub-classification of acute leukemias. [7]

From a prognostic point of view, aberrant antigen expression can adversely influence the clinical response, remission rate and overall survival in patients with acute leukemia.[3,5,7,8] In this study, the frequency of aberrant antigen expression in acute leukemia and its possible prognostic value is assessed in a cohort of patients treated at King Hussein Medical Center (KHMC) over the three years period.

Methods

This retrospective study includes cases of acute leukemia diagnosed over a-3 years period (January 2012 to December 2014). IT system of hematopathology department at KHMC revealed 368 cases of acute leukemia which were diagnosed during the study period using morphologic assessment of peripheral blood and bone marrow aspirate specimens and flow cytometry. Clinical and laboratory data including age at presentation, gender, blasts count and immunophenotypic analysis were collected. Only 212 patients out of 368 were followed up at KHMC and care of the other patients was carried out somewhere else. The 212 patients were evaluated during their treatment program and assigned into two groups: remission (group 1) and non-remission (group 2). Remission status was based on morphologic assessment of peripheral blood and bone marrow aspirate specimens at day 21 of induction therapy, completion of treatment and at onset of any clinical deterioration during the study period. The disease is considered to be in remission when blasts count was less than 5% of all nucleated bone marrow cells.[5,8]

Diagnosis of acute leukemia was established on the basis of morphology of leukemic cells and immunophenotyping analysis by multi parameter flow cytometry of peripheral blood fresh bone marrow aspirates. Peripheral blood and bone marrow aspirates were collected in EDTA tubes, stained with May-Giemsa and examined under light microscope.

The Becton Dickinson (BD) fluorescence activated cell sorter (FACS) Canto II was used for immunophenotypic analysis according to standard procedures. The analysis of CD45 expression combined with side scatter was used for gating strategy.[9,10]

Acute leukemia panel used in our laboratory includes antibodies with the following antigens: CD34, HLA-DR, TdT, myeloid panel (CD13, CD33, CD11b, CD11c, CD14, CD15, CD64, CD117, MPO), T cell panel (CD2, CD3, CD5, CD7, CD4, CD8), B cell panel (CD10, CD19, CD20, CD22,

CD79b).Cases of acute leukemia were typed as conventional myeloid, B cell or T lineage according to established WHO criteria (2008). However, cases having blasts either co-expressing more than one unexpected lineage associated antigen or under expressing lineage specific markers are designated to have an aberrant immunophenotype.[11]Immunophenotypic aberrancies in blast's populations were analyzed and reported. The cutoff limit for a particular marker to be positive was set at 20 %.[12]

The relationships between aberrant immunophenotypes with relapse and remission were analyzed using Chi-square (Pearson). Fischer exact probability test was used to calculate the P value. P-value of <0.05 was considered as statistically significant.

Results

A total of 368 cases of newly diagnosed acute leukemia, were included in the study. Patient's age ranged from 3 months to 89 years, with a mean age of 44.5 years, of which 183 patients were adults and 185 patients were < 14 years old. The male to female ratio was 1.4:1. Based on morphology and immunophenotypic analysis of leukemic cells, out of these 368 cases, there were 173 cases of ALL (47%) and 192 cases of AML(52%).Acute leukemia of mixed phenotype was detected in 3 patients (1%).ALL cases were further sub-classified into B-ALL in 131 cases (76%) and T-cell ALL in 42 cases (24%).

Of the total 368 cases, 272 (74%) cases of all acute leukemia cases have expressed conventional immunophenotypes as they showed the lineage specific markers while 96 cases (26%) showed expression of non-specific lineage markers. Out of 173 ALL cases, 50 cases (29%) showed myeloid associated antigens where as 44 out of the 192 AML cases (23%) have expressed lymphoid associated markers. These cases were considered as of aberrant immunophenotypes as shown in chart I.

In B-ALL, the commonest aberrant marker was CD33, noted in 18/38 (47%). This was followed by CD13 in 14/38 cases (37%) and double aberrant expression of CD13 and CD33 in 5/38 cases (13%). CD7 (T-cell marker) was co-expressed in only one case (3%) (Fig. I).Of the 12 T-ALL cases with aberrant marker expression, CD13 was seen in 5 cases (42%), followed by CD117 in 3 cases (25%) and CD33 in 2 cases (17%). Only one case (8%) expressed a B-cell marker CD79b. Double CD33 and CD13 expression was reported in one case (8%),as shown in Table I.

In AML,CD7 expressed in 19/44 cases (43%), CD 19 in 13/44 cases (30%), TdT in 3 /44 cases(7%), CD4 in 2 cases (4.5%) and CD 2 in 2 cases (4.5%) (Fig.2). Paired aberrant expression in AML, was as follow: CD7 and CD19 expression in 3 cases (7%), CD19 and cytoplasmic CD79b in one case (2%) andCD7 and TdTin one case (2%) (Table II). Following the French American British (FAB) classification of AML (1976), CD19 aberrant expression was most commonly seen in M2 (12/44) cases, followed by M0 and M1 (2 cases each) and one case of M5 and of M6. CD19 expression was absent in M3 and M7 cases. CD7 expression was seen in 9/44 cases of M1, 4/44 cases of M2, 3/44 cases of M0, 2/44 cases of M4 and 1/44 case of M5. No aberrant expression was seen in M3, M6 and M7 cases. Only 2 cases of FAB M0 expressed TdT (Table II).

Strict WHO 2008 criteria were adherent to for the diagnosis of MPAL. Only 3 cases were labeled as T/ myeloid (T/MY)MPAL where cytoplasmic CD3 and MPO were expressed in more than 20% of the gated cells.

On follow up of 212 cases during the study period, 117 cases were ALL and 95 cases were AML. Regarding ALL, 94 cases entered complete remission (group 1) of which 75 cases (80%) showed conventional markers while 19 (20%) had aberrant markers. 23 were in relapse (group 2) of which 7(30%) expressed conventional immunophenotypes and 16 (70%) showed aberrant immunophenotypes as shown in Table III. For AML, the study results showed that 50 cases were in remission (group 1) of which 42 (84%) showed conventional immunophenotypes and 8 (16%) expressed aberrant immunophenotypes. 45 cases presented with relapse (group 2), 21(47%) cases expressed conventional immunophenotypes and 24 (53%) had

Table I: Distribution of aberrant markers in acute leukemia.
(AML= Acute myeloid leukemia, B-ALL= B-cell acute lymphoblastic leukemia, T-ALL= T-cell acute

	AML	B-ALL	T-ALL
CD7	19 (43%)	1(3%)	
CD19	13 (30%)		
TdT	3 (7%)		
CD4	2 (4.5%)		
CD2	2 (4.5%)		
CD33		18 (47%)	2 (17%)
CD13		14 (37%)	5 (42%)
CD117			3 (25%)
CD79a			1(8%)
CD7/CD19	3(7%)		
CD19/CD79a	1(2%)		
CD7/TdT	1(2%)		
CD13/CD33		5(13%)	1(8%)

lymphoblastic leukemia)
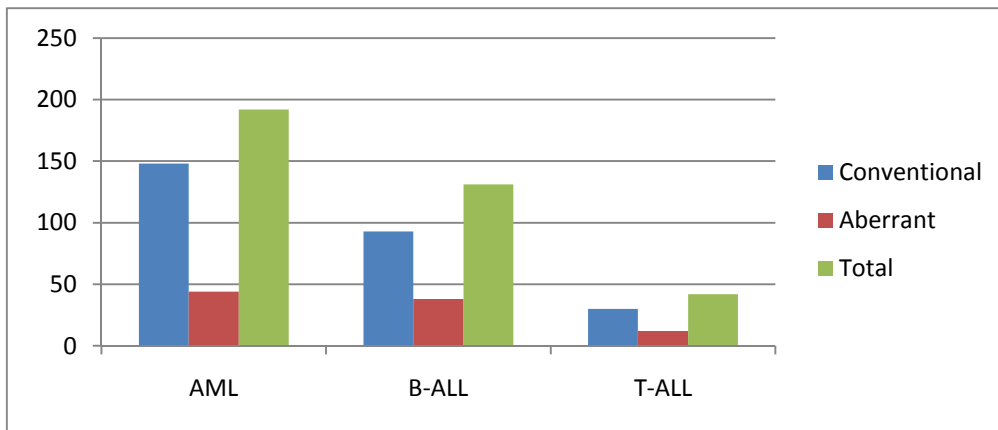

Chart I: Frequency of aberrant and conventional antigens expression in acute leukemia
(AML= Acute myeloid leukemia, B-ALL= B-cell acute lymphoblastic leukemia, T-ALL= T-cell acute
lymphoblastic leukemia)
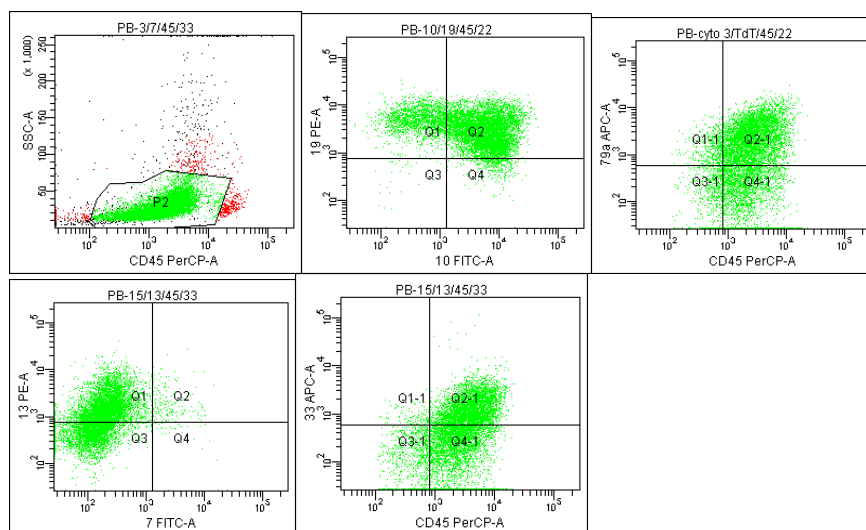
Fig. 1: Histogram of flow cytometry showed a case of B-cell acute lymphoblastic leukemia positive for the
following CD markers CD10, CD19, CD79a and co-expressing CD13 and CD33
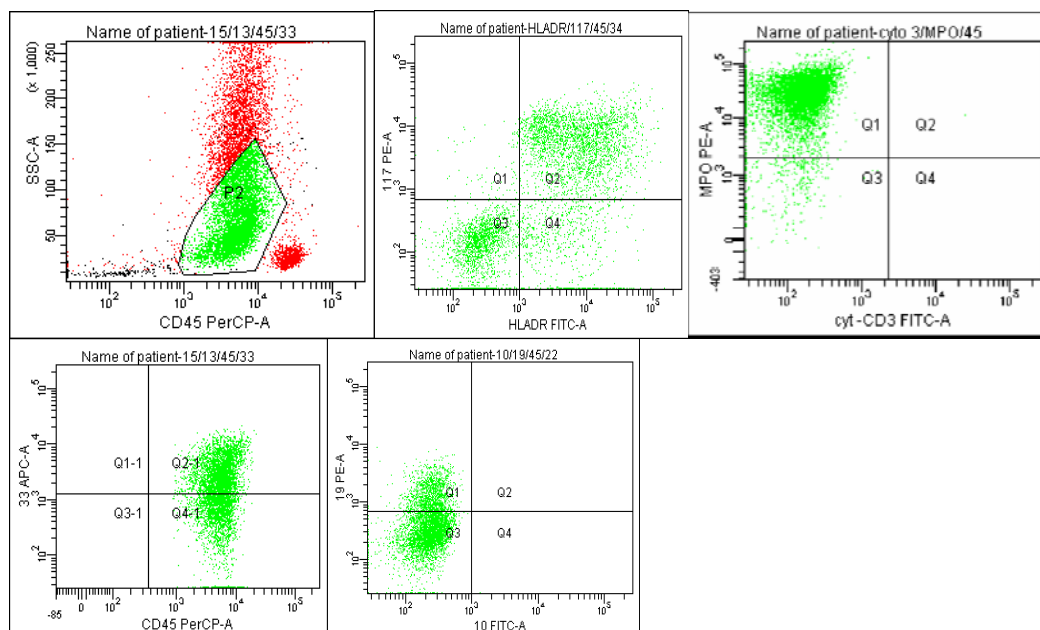
Fig. 2: Histogram of flow cytometry of case of AML expressing CD19 lymphoid marker

Table II: Frequency of aberrant lymphoid markers in AML subtypes according to FAB classification

AML-FAB	CD2	CD4	CD7	CD19	TdT
M0	0	0	3	2	2
M1	1	0	9	2	1
M2	0	1	4	12	0
M3	1	0	0	0	0
M4	0	0	2	0	0
M5	0	1	1	1	0
M6	0	0	0	1	0
M7	0	0	0	0	0

Table III: Outcome of follow up of ALL cases.

\ ALL	onventional	Aberrant	Rate	Risk ratio	Chi square	P value
Group 1 (remission)	75	19	0.202	0.29	21.47	<0.0001
Group 2 (non- remission)	7	16	0.695			

Group 1 who entered a complete remission. Group 2 who failed to enter in remission status

Table IV: Outcome of follow up of AML cases.

AML	onventional	Aberrant	Rate	Risk ratio	Chi square	P value
Group 1 (remission)	42	8	0.16	0.3	14.78	0.0001
Group 2 (non-remission)	21	24	0.533			

Group 1 who entered a complete remission. Group 2 who failed to enter in remission status

Table V: Requirements for assigning more than one lineage to a single blast population

Myeloid lineage

Myeloperoxidase (flow cytometry, immunohistochemistry or cytochemistry

or

Monocytic differentiation (at least 2 of the following: NSE, CD11c, CD14, CD64, lysozyme)

T lineage

Cytoplasmic CD3 (flow cytometry with antibodies to CD3 epsilon chain; immunohistochemistry using polyclonal anti-CD3 antibody may detect zeta chain, which is not T-cell specific)

B lineage (multiple antigens required)

Strong CD 19 with at least 1 of the following strongly expressed: CD79a, cytoplasmic CD22, CD10

or

Weak CD19 with at least 2 of the following strongly expressed: CD79a, cytoplasmic CD22, CD10

aberrant immunophenotypes as shown in Table IV.

We found that the rate of remission and relapse in aberrant ALL cases were0.202 and 0.695 respectively, with a Risk Ratio of 0.290,Chi square of 21.47 and P value of < 0.0001 which shows a significant correlation between the relapse rate and aberrant markers, as shown in Table III. Considering the AML aberrant cases, the rate of remission and relapse were 0.160 and 0.533 respectively with a Risk Ratio of 0.30, Chi square of 14.78 and P value of 0.00012 which also considered significant, as shown in Table IV.

Discussion

Acute leukemias are broadly classified into lymphoid B or T and myeloid lineages according to the characteristic antigenic profile of blasts. Immunophenotyping by multiparameter flow cytometry have improved the accuracy of diagnosis and sub-classification of acute leukemia since the prompt investigations and understanding of these cases can lead to dramatic progress in the management outcome and follow up program.[3,13]

The majority of acute leukemia cases express specific lineage markers; however, there is a variable number of cases in which aberrant immunophenotypes can be detected, and it is of clinical importance not only for the accurate diagnosis but also it has been shown to be useful in detection of minimal residual disease and for providing prognostic information.[6,13]The designation of MPAL has been proposed by 2008 WHO classification of acute leukemia as shown in Table V. [7]

In the present study, the immunophenotypes of blasts from 368 patients with acute leukemia were studied to determine the frequency of aberrant markers and their clinical prognostic relevance in this group of Jordanian patients. Out of 368 cases, 173 (47%) cases were of ALL and 192 (52%) of AML and 3 (1%) of MPAL. Male to female ratio equals 1.4:1, which is similar to that reported by other international studies.[3] The incidence of aberrant phenotypes has been reported in literature for both AML and ALL

with varying frequency ranging from 11% to 88%.[6,15]Our study reports the incidence of aberrant phenotypes in all cases of acute leukemia to be about 26% compared to 30% as reported by Khurram et al.[16]Launder TM et al. from Atlanta studied the incidence of one or more lymphoid antigens expression in AML which was seen in 22%. Amirghofran et al. stated that 30.2% of ALL cases showed aberrancy. [17,18] This is in agreement with our results in which the aberrancy was seen in 29% for each T and B-cell ALL cases and 23% in AML cases as shown in Chart I.

Regarding the aberrant antigens expression in B- cell ALL, it was shown that CD33 and CD13were the most common markers expressed in 47% and 37% respectively. CD7 was the only positive T-cell marker that observed in only one case 3% and none of the other T-cell antigens were positive in B-cell ALL in the current study. Our results are in accordance with that reported by Alkayed K et al, at King Hussein Cancer Center in Jordan, who studied the aberrancy in Jordanian children with B-cell ALL, and found that CD33 expression being the most common followed by CD13 and with regards to T-cell markers, CD7 was the only antigen expressed in B- ALL.[9] In contrast to Seegmiller et al, who demonstrated that CD13 was the most frequently marker expressed in B-ALL followed by CD33 and CD15. [12]

In T-cell ALL, CD13 was the most common antigen expressed in 42%, followed by CD117 (25%) and CD33 in about 17% while CD79a, which is a B-cell marker, was positive in only one case (8%). This is similar to that published by 2008 WHO classification which stated that CD79a may be observed in 10% of T-ALL cases and CD13, CD33 are expressed in 19-32%.[7] With regards to the paired aberrancy, our study showed that CD13 and CD33 were co-expressed in B-ALL and T-cell ALL in about 13% and 8% respectively.

Among the aberrant AML cases, we found that CD7 which is a T-cell antigen, was the most common aberrant marker expressed in 19cases (43%) in agreement with the results of Khurram et al. and Jahedi et al.[3,16] while in contrast to the results of El-Sissy et al. who reported that CD7 was expressed in a

minority of his cases. [19]Our study showed that CD7 was mostly confined to FAB AML-M1, M2 and M0 similar to that defined by 2008 WHO classification. [7] CD19 was expressed in 13 (30%) of our cases compared to 28% that reported by Sarma *et al.* from India.[6]Regarding the distribution of CD19in our cases, it was expressed mainly in AML-M2 as that reported by AbdulateefN *et al.* in KSA and also in agreement with Bahia et al. result.[13,20] According to TdT which is typical for lymphoblastic leukemia and lymphoma, we found 3 cases (7%) that were positive for this nuclear marker that mainly associated with more immature AML such as M0 and M1 similar to that reported by Venditti *et al.* from Italy. [21]In our study, CD2 was expressed in 2 cases (4.5%), in M1 and M3. And that for CD4, we have also 2 positive cases; one case for each M1 and M5 as shown by Abdulateef N *et al.* [13] Regarding the paired aberrancy, we found that CD7/CD19 present both in 3 cases (7%), CD19/CD79a in 1 (2%) and CD7/TdT in also one case (2%) which similar to other studies results.

In the present study, 3 cases (1%) were diagnosed as mixed phenotype acute leukemia of T/Myeloid type rather than having aberrant antigens, since they have met the EGIL and WHO criteria for mixed phenotype acute leukemia.

In our series, 117 cases of ALL were evaluated during the follow up period, there were 94 patients who achieved complete hematologic remission of which 20% had aberrant markers, while 70% of those who labeled as non-remission status, had aberrant immunophenotypes. Furthermore, the rate of remission and relapse in aberrant ALL was 0.202 and 0.695 respectively with a risk ratio of 0.290. So by comparing the ALL group who achieved remission with that who failed to enter a complete remission with regards to aberrant markers expression, there was a statistically significant difference between the two groups with a p value <0.0001. Based on these results, as shown by our study and most recent studies, aberrant myeloid markers expression in ALL may adversely affect achievement of complete remission and can be useful for prognostic evaluation in ALL.

In agreement with our study, there are many studies including those identified in Brazilian

patients by Lopes *et al.* and another study done in New York by Kurec *et al.* who demonstrated an association between aberrant myeloid expression in ALL and failure to achieve remission, which may identify them as a high risk groupespecially in children. [8,11] Others showed that it may be associated with adverse clinical picture at presentation and treatment outcome as identified by Abdulateef N *et al.* [13] However, there is still controversy about the relationship of myeloid markers expression in ALL and it's prognostic implication including the remission duration and survival as shown by other reports in which no prognostic significance was found for the presence of aberrant myeloid expression in patients with ALL (Jahedi *et al*).[3]

Regarding the followed up AML cases, there were 50 cases in remission of which 16% expressed aberrant markers and 53% of those who failed to enter in remission were seen to have aberrant immunophenotypes. The rate of remission and relapse were 0.160 and 0.533 respectively with a risk ratio of 0.30. By comparing these parameters, we found a significant correlation between aberrant phenotypes and predicting the remission and relapse status in AML (p value of 0.00012). So aberrant antigens expression in AML may be associated with low remission rate and can be considered a poor prognostic parameter in a significant proportion of patients.

Many international studies have shown a significant poor prognostic effect of aberrant lymphoid markers expression in patients with AML; Venditti *et al.* demonstrated that CD7 and TdT expression in AML was associated with unfavorable outcome and higher predisposition to minimal residual disease. [21]Even though, prior researches did not detect any significant impact of aberrant phenotypes on the prognosis of AML. [3]

In our study, there was no significant difference between conventional and aberrant phenotypes with regards to age, sex and blasts count. This was in consistent with a previous study performed in New York City. [11]Considering the cofounding variables that present in both study groups including age, sex, white cells count, cytogenetic patterns and response to the first induction therapy, which are strong predictors for survival in

acute leukemia, were not included in the current study.

Limitations of the study

Some potential limitations of this work must be mentioned. 156 patients (including 56 cases of ALL, 97 of AML and 3 cases of MPAL) were not followed upfor many causes including transfer to other centers, some died after diagnosis and others refused medical treatment. Therefore, larger scale study need to be conducted which should include other important variables especially the cytogenetic pattern, since some aberrant antigens may be related to a particular karyotype abnormality. Furthermore, additional markers which have important prognostic implications may be added such CD56.

Conclusion

The incidence of aberrant antigens expression in acute leukemia was comparable with the most published international data and it may represent a poor prognostic indicator among this group of Jordanian patients. These findings may help to assign patients with high risk group and low remission rate. Further studies are recommended to confirm the correlation of aberrant phenotypes in diagnosis, prognosis and therapeutic response of acute leukemia. Moreover, molecular cytogeneticstudies are recommended to shed light on potential biomarkers that might play a role in pathogenesis of antigen aberrancy, prognostic stratification and possibledrugable target.

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